(HypoPT) under routine clinical care. The secondary objective is to characterize the clinical course of chronic HypoPT under conditions of routine clinical practice. At enrollment, registry inclusion criteria are patients having a HypoPT diagnosis >6 months and receiving conventional therapy (CT; eg, calcium supplements and active vitamin D), rhPTH(1-84) plus CT, or rhPTH(1-84). We present baseline characteristics of patients as of a June 30 2019 data cut. Baseline was defined as the value entered at the time of enrollment (Visit 1). Baseline symptom data exclude patients who initiated rhPTH(1-84) prior to enrollment (n=68) and are herein presented as two groups: those subsequently prescribed with rhPTH(1-84) after enrollment or those treated with CT. All data are summarized descriptively. Patient data from 64 centers in Europe and North America were analyzed. In the analysis population (n=737), 587 patients (79.6%) were female, 620 (84.1%) were white, and the mean (SD) age was 49.1 (16.45) years. The mean (SD) BMI was 19.3 (5.73) kg/m^2 and 30.0 (7.72) kg/m^2 in patients aged <18 (n=25) and ≥18 (n=587) years, respectively. The primary cause of HypoPT was thyroid surgery (n=547 [74.2%]; of these, 281 [60.0%] underwent surgery for thyroid cancer). Endocrinologists were the prescribing specialists for most patients (n=660 [89.6%]). Vitamin D and analogs were prescribed for 90.1% of patients (calcitriol, 74.2%, native vitamin D, 47.4%, alfacalcidol, 7.9%,), calcium for 81.0% (calcium carbonate, 57.9%, calcium citrate, 27.1%), and thyroid hormones for 71.2% (levothyroxine, 73.4%; liothyronine, 5.8%). Symptoms reported at enrollment for the rhPTH(1-84) (n=66) and the CT groups (n=603), respectively, included fatigue (53.0%, 39.3%), paresthesia (48.5%, 29.2%), muscle twitching (48.5%, 21.1%), muscle cramping (40.9%, 33.0%), headaches (33.3%, 17.6%), anxiety (28.8%, 20.1%), muscle pain (28.8%, 19.2%), tetany (28.8%, 12.1%), and brain fog (27.3%, 16.3%). The baseline data for the overall population appear to be representative of patients with chronic HypoPT. Baseline data suggest that at enrollment patients prescribed rhPTH(1-84) after enrollment appear to have an increased burden of disease than patients receiving CT based on symptoms. PARADIGHM will be a valuable resource of real-world longitudinal data for patients with chronic HypoPT.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS I

Combination Immune Checkpoint Inhibitor Therapy for ACTH-Secreting Pituitary Carcinoma

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Introduction

Pituitary carcinoma is a rare yet serious entity with poor prognosis despite multimodal therapies. Cerebrospinal and/or systemic metastases are present by definition, making adjuvant systemic therapy necessary. Novel treatments are urgently needed for refractory cases. Immunotherapy with immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death 1 (PD-1) or its ligand (PD-L1) has been a revolution in multiple malignancies. The expression of CTLA-4 and PD-L1 has been elucidated in pituitary adenomas and could be implicated in pituitary carcinomas as well. Hypophysitis is also a frequent endocrine immune-related adverse event, especially during CTLA-4 blockade (with ipilimumab) or combination ICI. However, the efficacy of ICI in the treatment of refractory pituitary tumors has yet to be established. In 2018, Lin et al. successfully treated a first case of a hypermutated aggressive ACTH-secreting pituitary carcinoma with ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) combination immunotherapy.

Clinical Case

We report a 40-year old male, diagnosed with an invasive ACTH-secreting pituitary macroadenoma in 2012, initially treated by transsphenoidal and transcranial surgery, followed by adjuvant stereotactic radiotherapy and several courses of ketoconazole. In 2017, he presented to our clinic for a recurrent Cushing's phenotype despite maximal dosing of ketoconazole. Therapy both with pasireotide and cabergoline was unable to normalize cortisol levels and a bilateral (subtotal) adrenalectomy was performed. In June 2018, he presented to our emergency department with acute diplopia due to a left abducens nerve palsy. Imaging revealed recurrent invasion of the tumor into the sella turcica and cavernous sinus, together with cerebellar and drop metastases at the cervical spine. Temozolomide (TMZ) was initiated for a total of 9 cycles. Progressive disease was observed with development of new onset right oculomotor nerve palsy after the last TMZ cycle, and persistence of elevated serum ACTH-cortisol and urinary cortisol levels, despite the absence of radiological progression. Therefore, he was started in a compassionate use setting with a combination ICI therapy with ipilimumab 3 mg/kg and nivolumab 1 mg/kg (for 4 cycles), followed by maintenance nivolumab therapy (240 mg) every two weeks. He has stable disease (both radiographically and hormonally) five months after the initiation of the immunotherapy.

Clinical Lesson(s) or Conclusion(s)

We report the second case of ACTH-secreting pituitary carcinoma treated with combination ICI therapy. The disease status of the patient is stable up until now, suggesting at least disease control by the immunotherapy. Checkpoint blockade inhibitors are a promising novel treatment modality for refractory pituitary tumors and should be further studied.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Integrative Single-Cell Transcriptomic and Epigenomic Landscape of Mouse Anterior Pituitary Cell Types

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SAT-298

The pituitary gland is a critical regulator of the neuroendocrine system. To further our understanding of the classification, cellular heterogeneity, and regulatory landscape of pituitary cell types, we performed and computationally integrated single cell (SC)/single nucleus (SN) resolution experiments capturing RNA expression, chromatin accessibility, and DNA methylation state from mouse dissociated whole pituitaries. Both SC and SN transcriptome analysis and promoter accessibility identified the five classical hormone-producing cell types (somatotropes, gonadotropes (GT), lactotropes, thyrotropes, and corticotropes). GT cells distinctively expressed transcripts for *Cga*, *Fshb*, *Lhb*, *Nr5a1*, and *Gnrhr* in SC RNA-seq and SN RNA-seq. This was matched in SN ATAC-seq with GTs specifically showing open chromatin at the promoter regions for the same genes. Similarly, the other classically defined anterior pituitary cells displayed transcript expression and chromatin accessibility patterns characteristic of their own cell type. This integrated analysis identified additional cell-types, such as a stem cell cluster expressing transcripts for *Sox2*, *Sox9*, *Mia*, and *Rbpms,* and a broadly accessible chromatin state. In addition, we performed bulk ATAC-seq in the LβT2b gonadotrope-like cell line. While the FSHB promoter region was closed in the cell line, we identified a region upstream of *Fshb* that became accessible by the synergistic actions of GnRH and activin A, and that corresponded to a conserved region identified by a polycystic ovary syndrome (PCOS) single nucleotide polymorphism (SNP). Although this locus appears closed in deep sequencing bulk ATAC-seq of dissociated mouse pituitary cells, SN ATAC-seq of the same preparation showed that this site was specifically open in mouse GT, but closed in 14 other pituitary cell type clusters. This discrepancy highlighted the detection limit of a bulk ATAC-seq experiment in a subpopulation, as GT represented ~5% of this dissociated anterior pituitary sample. These results identified this locus as a candidate for explaining the dual dependence of *Fshb* expression on GnRH and activin/TGFβ signaling, and potential new evidence for upstream regulation of *Fshb*. The pituitary epigenetic landscape provides a resource for improved cell type identification and for the investigation of the regulatory mechanisms driving cell-to-cell heterogeneity.

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Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Utilization of GluCEST, a Novel Neuroimaging Technique, to Characterize the Brain Phenotype in Hyperinsulinism/Hyperammonemia Syndrome

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MON-110

Background: Hyperinsulinism/Hyperammonemia (HI/HA) syndrome is the second most common form of congenital hyperinsulinism. It is caused by gain-of-function mutations in glutamate dehydrogenase (GDH), a mitochondrial enzyme expressed in pancreatic β-cells, liver, kidney, and brain, and is responsible for metabolizing glutamate into α-ketoglutarate and ammonia. In addition to hyperinsulinemic hypoglycemia due to abnormal GDH activity in pancreatic β-cells, ~80% of patients have developmental delays, learning, or behavioral disorders and >60% have atypical absence seizures (Bahi-Buisson, 2008). These neurologic symptoms are not fully explained by hypoglycemia and are hypothesized to result from central nervous system (CNS) glutamate imbalance due to CNS GDH overactivity. Newer magnetic resonance imaging (MRI) techniques have allowed for sensitive estimation of CNS glutamate using Glutamate Chemical Exchange Saturation Transfer (GluCEST). We aimed to comprehensively characterize the biochemical and clinical neurologic phenotype of HI/HA leveraging GluCEST MRI.

Methods: Subjects with confirmed HI/HA diagnosis and without contraindication to MRI had electroencephalogram (EEG), serum ammonia, and the following validated neurodevelopmental assessments: ABAS-3, BRIEF, and ASEBA CBCL (if <18 years) or ASR (if >18 years) completed. GluCEST MRI axial hippocampal and midsagittal slices were acquired on a 7.0T Siemens scanner and reported as GluCEST % contrast. Healthy control GluCEST % contrast data were obtained from a separate study using the same neuroimaging protocol.

Results: 8 HI/HA subjects (4 female; mean age 28 years [range 16-56] years) participated to date. Median serum ammonia was 58 umol/L (IQR 39-89). 50% self-reported learning impairments and 37.5% self-reported prior ADHD diagnosis. Marked unilateral increase in hippocampal GluCEST % contrast was observed in 3/6 subjects (2 L>R; 1 R>L). Overall, median peak GluCEST % contrast level was significantly higher in HI/HA subjects than controls (10.3% [IQR 8.9-11.3] v. 8.0% [IQR 7.8-8.4], p=0.0013, n=6).

Conclusions: This is the first study to evaluate CNS glutamate via GluCEST in HI/HA. Hippocampal glutamate, measured by GluCEST % contrast, was significantly higher in HI/HA subjects than healthy controls. Laterality in hippocampal glutamate was observed in half of subjects. These findings are remarkable given the known role of abnormal glutamate signaling in the development of epilepsy and neurocognitive impairment. Next steps are to complete midsagittal GluCEST image processing, EEG and neurodevelopmental assessment interpretations to explore correlations between CNS phenotype and brain glutamate pattern. GluCEST holds promise for elucidating the pathophysiology of CNS manifestations in HI/HA syndrome.